REMARKS

A. Status of the Claims

Claims 1-3, 9-15, 20-21, 24, 30-32 and 35-45 are pending and currently under examination.

B. Rejections On the Basis of Alleged Non-Enablement

On page 3, the Action first rejects all of the claims under section 112, first paragraph, taking the position that the specification fails to enable the following: the use of any muscle specific promoter to obtain a stable transgenic fish line suitable for the ornamental fish market showing fluorescence upon exposure to sunlight; any transgenic fish showing more than one fluorescent protein in the same tissue to effect a new fluorescent color that is visible after exposure to sunlight; and mating fish across genera or family.

"Any muscle specific promoter"

With respect to the "any muscle specific promoter" issue, Applicants provide a declaration of Zhiyuan Gong, Ph.D. ("Gong Declaration") to support that the claims are enabled. The Gong Declaration stated that "B[b]ased on my knowledge and experience in the production of fluorescent, transgenic fish, it is my opinion that virtually any muscle-specific promoter can be employed to produce very highly fluorescent founder embryos and lines." (Gong Declaration, para. 6).

The Action's position that the specification only teaches that the fast skeletal muscle isoform of myosin isoform light chain 2 gene promoter comprising SEQ ID: No 22 showed strong enough fluorescence expression is incorrect. As acknowledged by the Action, "the specification has contemplated that methods of the invention may be used to create transgenic fish of any species using any muscle specific promoter." For example, the present specification

discloses at least two constructs containing promoter fragments (2011 bp (SEQ ID:22) and 1338 bp) capable of maintaining a high level of expression (Specification, para. [0089]). In addition, the specification has also identified that under MCK promoter, "about 12% of surviving embryos expressed GFP strongly in muscle cells ... The GFP expression was always found in many bundles of muscle fibers." (Specification, para. [0082]).

This is also supported by the Gong Declaration, which pointed out that "in Example III the specification teaches that one can screen the transgenic fish embryos to select those embryos exhibiting the desired expression characteristics. Particularly, preferred are those embryos exhibiting high expression such that the fluorescence is visible in the sunlight. I would also direct attention to Figures 8 through 12, particularly Figure 12, and their associated figure legends." (Gong Declaration, para. 5).

In general, position effect frequently affects expression of a transgene in spite of a strong promoter; however, while it may well be necessary in some instances to use one of the above or other screening procedure that permits one to select those embryos that have appropriate position effects, this should require only reasonably routine repetitive steps. Considering the muscle occupies a large part of the fish body and thus has the capacity to synthesize enough proteins for visible fluorescence, screening for visible fluorescence using any muscle-specific promoter provides specific guidance and predictable results for obtaining stable transgenic fish suitable for the ornamental fish market (Gong Declaration, para. 6).

Thus, in view of successful working examples of muscle specific promoters that may be used in the claimed method and specific guidance with regard to making and using of any muscle specific promoters that may be used in the claimed method, the present specification enables those of ordinary skill in the art to practice the claimed method.

We would also refer the Examiner to various articles of record which demonstrate that other muscle specific promoter can be used in the claimed method. As in the Gong Declaration, for example, the Examiner is referred to the attached article of Kinoshita entitled "Transgenic medaka with brilliant fluorescence in skeletal muscle under normal light" (*Fisheries Science, 70*:645-649, 2004) (Gong Declaration, para. 7). As the title implies, this article describes the preparation of transgenic, fluorescent medaka having a brilliant fluorescence in skeletal muscle under normal light. In these studies, the author employed the skeletal muscle actin promoter. Further, on page 648, col. 1, the author also mentions the article of Chou *et al.* (*Transgenic Res., 10*: 303-315, 2001), which is said to teach transgenic medaka strains with the GFP gene under the control of the β-actin gene regulatory region, which could be observed under daylight.

Furthermore, the evidence put forward by the Examiner does not support the position of non-enablement. The relevance of the Hackett reference (1993) is not at all understood. Hackett merely stands for the proposition that some fish regulatory elements have been developed but none of them direct muscle specific expression. The same can be said for Kuo *et al.*, which demonstrates that cis-acting elements from the mouse carcinoma nectin neurofilament gene was effective in directing either neuron-specific or skin-specific expression, but not muscle specific expression. See also, Kim *et al.* reference.

The Higashijima reference merely stands for the position that those of skill in the art were aware that certain design or screen choices may need to be made in order to achieve an optimally performing transgenic fish with muscle specific promoters. This is not a proper basis for raising an enablement concern. Indeed, as mentioned above in the Gong Declaration, Chou *et al.*, which is said to produce transgenic medaka strains with the GFP gene under the control of the β-actin gene regulatory region observes green fluorescence under daylight (Kinoshita, page 648). This

evidences that something "does not work well" in one case (it may work in another case) does not lead to the conclusion that the present invention is not enabled for the preparation of any transgenic using any promoter.

Turning to Gong *et al.* (2003), it also does not support non-enablement. Gong stated in his declaration: "I further understand that in connection with the above-mentioned rejection, the examiner relies on a statement from page 62, col. 2, of my 2003 BBRC publication, with respect to which the examiner states that:

> It is clear from the teaching of Gong et al that strong expression of a fluorescent gene under the control of MLC2 promoter in muscle tissue that constitutes majority of the fish body tissue is vital for successfully generating transgenic fish for distribution in ornamental fish market.

This is not a true statement. As can be seen from reading the excerpt referred to by the examiner, it merely stands for the proposition that "one" consideration is the strength of the promoter, and that another consideration is the tissue specificity, with muscle promoters in general being preferred for this reason. However, nowhere does the article in any way state or imply that the MLC2 promoter is "vital" to producing our fluorescent transgenic fish. As explained above, we know that this particular promoter is not "vital" in this regard. (Gong Declaration, para. 8).

Last, the Examiner is referred to the enclosed review article of Hackett *et al.*, "The Molecular Genetics of Transgenic Fish," which was published in 2000 at about the same time as the filing of the present application. This review article sets forth an abundance of tissue specific and other promoters that were all routinely found to be operable in fish. See, for example, Tables 1 through 3.

"More than one fluorescent protein in the same tissue"

Using the claimed method to provide transgenic ornamental fish that "more than one fluorescent protein is expressed in the same tissue," a subject matter comprised in dependent claim 30, has been rejected by the Examiner for alleged lack of enablement. Applicants respectfully transverse.

In response, Applicants find that the specification provides guidance as to how to provide transgenic fish with more than one fluorescent proteins in the same tissue, for example, in paragraph [0092].

"Mating fish between different genera and families"

In response, Applicants first note that the evidence put forward by the Examiner actually supports the position of enablement of this claimed subject matter comprised in dependent claim 36. Bartley *et al.* fully evidences the broad knowledge in the art for making inter-specific hybrids. Note that the excerpt relied upon by the Examiner merely states that "inadvertent hybridization and backcrossing can lead to unexpected and undesirable results (emphasis added)" Therefore, careful design in routine practice could avoid these problems.

Furthermore, enablement is not precluded by the necessity for some experimentation such as routine screening. "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

C. Rejections On the Basis of Written Description

The Action next enters a written description rejection of all the claims on the basis that the specification is alleged to fail to provide an adequate written description of the use of any muscle specific promoters in the preparation of any fish.

"Any muscle specific promoter"

The present specification teaches that isolation of muscle-specific zebrafish cDNA clones, determination of their expression patterns, and isolation of muscle-specific promoters in Examples I-II. MCK and MLC2f promoters are specifically identified as examples of muscle specific promoters used to provide transgenic fish to the ornamental fish market (Example III, FIGs. 8-12).

Moreover, there is no legal basis under the written description requirement that an applicant set forth in the claims the specific structures being claimed where, as here, the class of compounds being claimed are known to the prior art. Instructive in this regard is *Capon v. Eshhar v. Dudas*, 418 F.3d 1349, 76 USPQ2d 1078 (Fed. Cir. 2005). The fact that muscle specific promoters were well known as of the filing date is evidenced by evidence set forth above in the enablement section of this response.

"Preparation of any fish"

"[A] patent need not teach, and preferably omits, what is well known in the art." *Hybridtech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1987). In response, Applicants first note that many, many different species of fish have now been genetically engineered such that now the genetic engineering of fish is generally routine. This is noted in the present specification at paragraph 5.

Furthermore, the present specification discloses that the chimeric gene constructs demonstrated successfully in zebrafish in the present invention should also be applicable to other fish species (para. [0085]).

Indeed, the Action acknowledges that "the transgenic fish comprising chimeric gene under control of MLC2f promoter could be demonstrated as possessed for the contemplated biological fact" (Action, page 14; emphasis added).

D. Non Statutory Double Patenting

The Action lastly provisionally rejects claims 1-3, 9-15, 20-21, 24, 30-32 and 35-42 over claims 1-7 of copending Application No. 11/749,032 on the basis of alleged non-statutory obviousness-type double patenting and also rejects claims 1-3, 9-16, 19-21, 24, 30-32 and 35-42 over claims 1-7 of U.S. Patent 7,135,613 on the basis of alleged non-statutory obviousness-type double patenting.

In response to double patenting over U.S. Patent 7,135,613, Applicants respectfully traverse. Applicants note that during the prosecution of USSN 09/913,898, Applicants attempted to introduce claims consistent with the claims pending in the present application. See Applicant's Amendment dated May 9, 2003. In response to this attempted amendment, the Examiner refused entry of the amendment: "The amendment filed on May 12, 2003 ... presenting only claims drawn to a new invention is **non-responsive** (MPEP §821.03) (underline added)," taking the position that such claims were found not to be drawn to the invention elected in that case, which later became the '613 patent. See Restriction Requirement mailed 12/18/03 and, again, the Restriction Requirement dated 7/30/03. Thus, the PTO has already decided that the present claims are patentably distinct. It is thus requested that the double patenting rejection be withdrawn.

A provisional double-patenting rejection is not a final rejection that blocks the prosecution of all of the conflicting applications. If a provisional double-patenting rejection is the only rejection remaining in an application, the Examiner should withdraw the rejection and

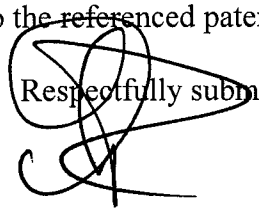
permit the application to issue as a patent. MPEP § 804(I)(B). After one application issues as a patent, the provisional double-patenting rejection in the remaining application is converted to an actual double patenting rejection. Id. Thus, either the present application or the copending application must issue as a patent before an actual double patenting rejection may be raised against the remaining application.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

The Examiner is invited to contact the undersigned attorney at (512) 536-3055 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Date: October 7, 2008